Physiology of Breathing and Related Pathological Processes in Infants

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There is little information describing control of breathing in the fetus and infant. The available data have largely been drawn from studies in animals and awake adults. Although the hierarchy of control of breathing is the same in adults and infants, feedback emphasis is different, with behavioral states and the sleep/wake cycle primary in the fetus and infant and integrated chemoreceptor response primary in the older child and adult. Control of breathing during the transition from the fetal state to a breathing child and the process of maturation are very different from that in adults. The article begins with an overview of the changes in the systems responsible for breathing at the developmental stages from fetus to neonate, with differences highlighted. It then discusses the possible pathology related to difficulties in negotiating this transition period, including apnea, sudden infant death syndrome, and chemoreceptor control abnormalities.
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MUCH OF the data on breathing in infants and children is drawn from comparisons to fetal animals or derived from the literature on adult studies. Breathing control in adults and children are similar in many respects; there is hierarchal control (cerebrum to brainstem to effectors) and a feedback system, and respiration is adjusted according to the metabolic need of an activity or state (Fig 1). Two major differences distinguish breathing control in adults and infants: (1) the change from the fetal state with a metabolic dependence on the placenta to postnatal gas exchange (breathing) and (2) the incomplete development of the central nervous system; upper airway, lungs, and respiratory muscles; and chemoreceptors at birth. These systems continue to evolve until full maturation is reached. Cellular, neuropharmacologic, and molecular systems undergo modification as well.

Disorders of breathing are likely to occur at birth because of the need to completely change the mode of respiration and rely on an "untested" system. Breathing disorders may also appear during the maturation period (usually the first few months of life). Pathological processes become apparent as the child attempts to adapt to the new environment. In what follows we briefly review normal developmental changes and then discuss pathological processes related to these systems.

NORMAL DEVELOPMENT

Fetal "Respiration"

The Controllers

The central respiratory neurons lie in the brainstem, within complexes known by their location as the dorsal respiratory group, ventral respiratory group, and pontine respiratory group. Migration of nerve cells to these areas appears to occur between 10 and 20 weeks gestation, but differentiation and network formation continue throughout the neonatal period.[1] Synaptic connections in these nuclei actually increase before birth, presumably duplicating processes to ensure a safe transition, and then decrease gradually after birth, weeding out unnecessary pathways.[2]

The Effectors

Organized, rhythmical contractions of the diaphragm first appear in the fetus at 10 to 12 weeks gestation.[3] The movements are episodic and increase in frequency with age up to 30 weeks, occupying approximately 30% to 60% of the fetal day at term.[4] The diaphragm is the primary muscle of "breathing" during fetal life. The dilator muscles of the upper airway, the posterior cricoarytenoid and the genioglossus muscles, exhibit activity that is augmented during gasping movements.[4]

The fetal lung is fluid-filled and does not participate in metabolic activity.[4] The flux of fluid in and out of the fetal lung is governed by the amount produced, "breathing" movement (or its absence), and a relatively high upper airway resistance that in the healthy fetus results in a dominant outward movement.[4]

The Sensors

Even in utero, a feedback system modulates fetal "breathing" movements. These movements be-

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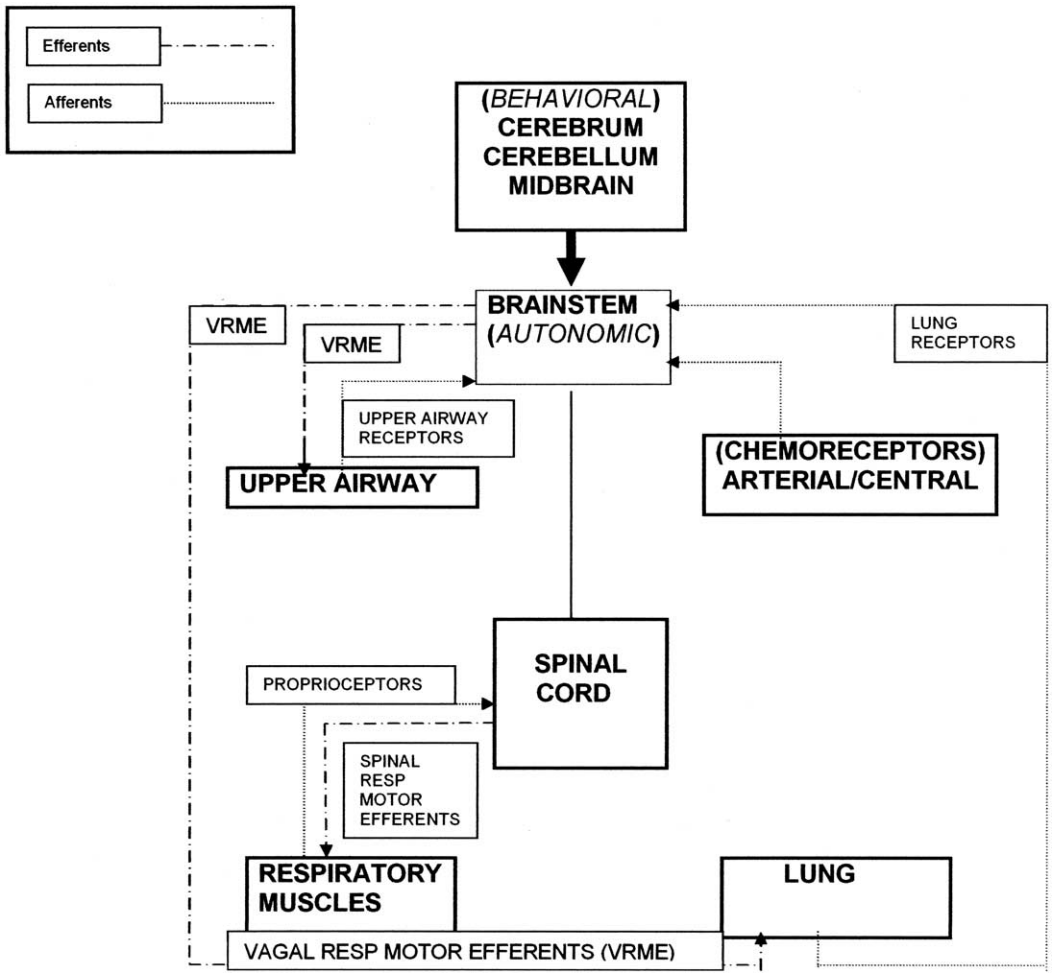

Fig 1. Schematic representation of the control of breathing showing the interactions of the controllers, effectors, and sensors. (VRME = vagal respiratory motor efferents).

come greater with higher CO_2 levels, increased metabolic rate, and improved energy supplies (from good nutrition).[4] Hypoxia in the fetus depresses respiratory movements, as well as other motor movements. This appears to be mediated via the pons rather that by peripheral chemoreceptors, because it occurs in animals even if the carotid bodies are removed.[4,5] The central chemoreceptors appear to be very active during fetal life and drive the response to CO_2 and blood pH levels.

The Suprapontine

The behavioral influence of the suprapontine structures and sleep/rest cycle of the fetus dominate all other systems. Cycles of respiratory activity are correlated with the sleep/wake cycle in the fetus with "breathing" movements during active "sleep" and the absence of breathing movements in the high-voltage, slow-wave "sleep" state.[6]

The First Breath

The specific mechanisms that allow the transition from a fluid-filled state with minimal blood flow, intermittent activity, and erratic control to a continuously functioning system governing metabolic control are unknown. Failure of this transition results in death unless artificial ventilation is provided.

The Controller

Initiation of respiration is an extremely complex process, possibly triggered by the interaction of

acute and prolonged hypoxia occurring with the separation from the placenta and transition through the birth canal. Synergistically acting arousal stimuli, such as light, gravity, cold, sound, and touch, appear to assist in the process. Other possible contributing mechanisms include removal of inhibition by a higher center and/or the alteration of central chemoreceptors by neuropharmacologic agents. There is some evidence for this second mechanism. Agents such as prostaglandin E_2 are produced in large quantities by the placenta and become inactive after birth. Catecholamines are also secreted during the birth process, possibly stimulating breathing.[6,7] Continuous breathing can also be initiated in the fetal lamb if the arterial partial pressure of oxygen (PaO_2) is increased via an endotracheal tube or if the cord is clamped (keeping the PaO_2 and partial arterial pressure of carbon dioxide [$PaCO_2$] unchanged).[8] Although different processes may stimulate breathing, the actual mechanism remains unknown.

The Effectors

A negative pressure of 40 to 100 cm is required to initiate respiration; this is generated by the diaphragm.[9] This effort persists for several breaths after birth. Following this is a period of rapid, irregular breathing with grunting that typically lasts less than 24 hours.[10] The fluid clears from the lungs, with a small amount expelled through the upper airway during the birth process. However, this clearing of fluid occurs over the first few hours, regardless of whether the method of delivery was vaginal or through caesarean section.[11] The functional residual capacity (FRC), the volume of gas in the lungs at the end of a normal expiration, is equivalent to the oxygen stores of the infant lung.[2] This volume increases over the first 2 days of life from 15% of the eventual amount to approximately 100 mL, or 30 mL/kg in the average neonate.[12]

The Sensors

The peripheral chemoreceptors require adjustment to a higher PaO_2 at birth. This is normally completed by 24 to 48 hours after birth, but can be delayed in infants with chronic hypoxia.[13,14] The response to CO_2 by the carotid bodies and central chemoreceptors is similar to the response in adult humans. Minute ventilation increases linearly in response to higher CO_2 levels. The maximum minute ventilation does not exceed 3 to 4 times baseline because of the characteristics of the airway and chest wall in the infant.[15] Reflexes originating in the lung and airway also participate in the first breath. Rapid inflation of the lung may trigger irritant receptors and provoke Head's paradoxical reflex, causing a prolonged inspiration rather than expiration.[7] Stimulation of unmyelinated pulmonary fibers by elevated interstitial pressure causes rapid, shallow breathing that aids fluid absorption and may also initiate breathing.[10]

Neonatal Life

The Controllers

The central neuronal network is not fully organized at the time of birth, and maturation proceeds rostrally from the brainstem.[16] The maturity level of this central network is the primary determinant of the neonate's response to stimuli. For example, maturity of the brain stem auditory-evoked responses correlate negatively with the presence and frequency of apnea in preterm infants. These neurons inhabit the same part of the brain stem as the respiratory center, implicating disorganization or immaturity of the respiratory centers as the cause of apnea.[17]

Experiments in fetal animals have investigated the neuroactive substances in the brain. Inhibitory agents, such as the neuropeptide somatostatin and amino acids gamma-aminobutyric acid and taurine, dominate in the low fetal PaO_2 present before birth. Whether other neuroinhibitors, such as the endogenous opioids, play a role remains unclear. Neurostimulators, such as the amino acids glutamate and aspartate, the neurotransmitter noradrenaline, and the neuropeptide substance P, increase after birth, and their activity is enhanced by the higher PaO_2 levels.[16] It is assumed that the neurochemistry of the neonatal brain undergoes both an immediate and a longer-term redistribution of synaptic neurotransmitters similar to that observed in rabbits after birth.[18]

Changes in the central rhythm generator occur immediately after birth. Firing of neurons from the nucleus reticularis rostroventrolateralis occurs just before inspiration in newborn rats.[19] The inspiratory time gradually increases from <100 msec to >400 msec as adulthood is reached.[20,21] Expiratory neurons undergo a marked increase in function after birth, after development of the inspira-

tory network.[16] Excitation of these expiratory neurons increases with age.

The Effectors

The pharyngeal airway is narrower in an infant than in an adult. In the infant the soft palate and base of the tongue are apposed, to generate negative pressure for sucking.[10] The infant's upper airway is susceptible to collapse because of its small diameter and poor structural support. The epiglottis is large, the tongue lies in a horizontal position, and the hyoid and larynx are elevated. In the normal infant, the muscles of the upper airway, chest wall, and diaphragm are coordinated and activate sequentially, allowing active breathing. Deviations from normal, such as immaturity of the receptors of the upper airways, absence of a coordinated response to stimulation, or absence or suppression of the upper airway sensory input, can result in apnea. The airway appears to be narrower at 6 weeks of age than at birth.[21,22] Over the first 2 years of life, the upper airway grows in size and changes configuration with gradual movement of the larynx and hyoid bone downward.[22] These changes decrease the likelihood of upper airway obstruction.

The muscles of the infant's chest wall are weak and operate at a mechanical disadvantage because of the oblong (as opposed to elliptical) shape of the chest, elevated compliance of the chest wall, and horizontal placement of the diaphragm. Ventilation is maintained by increasing respiratory rate rather than volume. The infant's oxygen stores are diminished compared with the metabolic needs because of the low FRC; this situation begins to reverse at age 3 months, when the chest wall becomes less compliant. Abdominal muscles also are relatively weak and provide little support or stability.

Breathing is also complicated by the fact that the infant spends much time lying down and asleep. Thus the infant's diaphragm lacks a fulcrum for power generation (a function of the strong abdominal muscles in the older child and adult). During active, or rapid eye movement (REM), sleep, the muscles of breathing (except the diaphragm) are paralyzed, thus making this disadvantage more significant. In the infant, REM sleep accounts for more than 50% of total sleep time.

The infant's head and eyes are nearly adult size. Facial growth primarily affects the nasal and oral airway. The face is 60% of adult size by age 4 years and 90% structurally complete by age 12 years.[23]

The Sensors

The mechanoreceptors in the lung provide feedback to the central receptors through the vagus nerve and maintain appropriate ventilation in the newborn. Vagotomy disrupts normal ventilation in the newborn rat but has no effect on the adult rat, suggesting that this feedback is critical for maintenance of normal breathing in the neonate.[24]

Central chemoreceptors respond to high CO_2 levels similarly in the neonate and the adult, although the neonate has a lower resting CO_2 level. A drop in temperature also enhances the neonate's response to CO_2. Hypoxia depresses the breathing response to CO_2 in the neonate.[16]

The peripheral chemoreceptors reset to a higher PaO_2 during the first week of life. Dopamine is likely involved with this change, because these levels rise concomitant with the responsiveness of the receptors. The importance of these chemoreceptors in increasing ventilation in response to hypoxia grows over the first few weeks of life. In a study on fetal sheep, absent peripheral chemoreceptors did not appear to be associated with problems at birth but did result in sudden death of the lamb after a few weeks.[25] Experiments suggest a progressively increasing response of the peripheral chemoreceptors to CO_2 during the first 3 months of life.[26]

The neonate's response to acute hypoxia is biphasic, with first a transient increase in ventilation and then a decrease in minute ventilation. This decrease (in contrast to the response in an adult) is associated with a similar decrease in metabolism that allows the infant to tolerate hypoxemia.[10]

Pulmonary stretch and irritant receptors are most active in the newborn and preterm infant and do not seem to contribute to ventilation in the adult. These receptors may mediate reflexes crucial to maintaining lung volume in the infant, who has a highly compliant chest wall. The stretch receptors are responsible for the Hering-Breuer inflation reflex (ie, termination of inspiration in response to lung distention). This reflex is believed to prevent lung emptying by maintaining a high respiratory rate; it also appears to assist in active exhalation at high lung distending pressures. A second reflex, known as Head's paradoxical inflation reflex, is mediated by irritant receptors and occurs only in

newborns. In response to a rapid inflation occurring during a respiratory effort, this reflex triggers, rather than inhibits, further inspiration. Other receptors are less well delineated. C-fiber receptors, stimulated by edema, are believed to be responsible for apnea associated with tachypnea, bronchoconstriction, and laryngeal constriction. Pulmonary vagal receptors control the opening of the laryngeal aperture and help maintain FRC.[10] The preterm infant responds to airway stimulation with slowing of respiration.[16] The cough reflex does not become fully developed until an infant reaches term; however, the neonate has extremely strong upper airway protective reflexes, and irritation by liquid in the airway will trigger reflex apnea.[10] The largest and primary populations of lung airway receptors are the slowly adapting receptors (SARs) and the rapidly adapting receptors (RARs). SARs regulate the breathing pattern, and RARs are involved with airway defenses. The neonate airway contains fewer SARs and less active RARs than the adult airway.[10]

The Suprapontine

The autonomic control of breathing is superseded by voluntary mechanisms in the awake adult and infant. Sleep/wake cycles are present before birth, but become progressively better delineated afterward. Circadian rhythms are established during the first few months of life, dependent more on chronological age than on gestational age.[23] Brain stem reticular activity drives respiratory movements in the preterm and neonate during REM sleep independent of the metabolic feedback. However, chemical control drives respiration during quiet, or non-REM (NREM) sleep. Breathing is less efficient during REM sleep than during NREM sleep due to the poor muscle tone in most of the muscles of respiration, the loss of upper airway tone, and irregular breathing patterns. This combination of factors predisposes the infant to airway obstruction.

Input from the hypothalamus increases ventilation in the overheated fetus, whereas exposure to increased temperatures in preterm and term neonates decreases ventilation and may cause apnea.[16] A change in environmental temperature can cause unpredictable changes in respiration because of potential changes in metabolism. The presence or absence of nutrients, such as glucose and amino acids, can also alter respiratory activity.[16]

The ability to arouse from sleep with stimulation is crucial to survival. Hypoxia, apnea, temperature, blood pressure, and chemical stimulation of the larynx are all stimuli that should cause arousal. This response to stimulation may vary, however, depending on sleep stage, age, and level of neurologic maturation. Neurologic maturation can be extremely variable. By age 3 months, REM sleep decreases and stage 2 and delta NREM stages sleep are easily distinguished. Arousal thresholds to irritants and hypoxia decrease from birth to age 3 months.[27]

The infant is especially susceptible to a variety of breathing difficulties. Breathing problems related to size, discoordination, or immaturity often resolve with increasing age, but can be life-threatening in the newborn.

PATHOLOGICAL PROCESSES AFFECTING CONTROL OF BREATHING

Apnea

The most common disorder of breathing control in neonates, apnea (cessation of breathing) can be central, obstructive, or mixed. Central apnea is characterized by absence of breathing effort and thus absence of airflow. Obstructive apnea is marked by breathing effort with no airflow. Mixed apnea involves some combination of central and obstructive features. An apparent life-threatening event (ALTE) in an infant describes an episode (witnessed by an observer) characterized by some combination of apnea, color change, and change in muscle tone. About 5% of children who die of sudden infant death syndrome (SIDS) have experienced such an event.[28]

Central Apnea

Central apnea can occur normally and often is of no physiological consequence. An earlier reported association of central apnea with SIDS was subsequently shown to be based on inaccurate data.[29] Central apnea of clinical consequence (ie, apnea associated with desaturation or with an ALTE) is almost always associated with a central nervous system (CNS) abnormality, either structural or functional (Table 1). Lesions producing pathological central apnea can be located in the spinal column or in the brain stem. Primary muscle disease and metabolic abnormalities may be associated with profound weakness and may cause apnea

Table 1. Causes of Central Apnea

Level	Name/cause	Type of Defect
Suprapontine	Lissencephaly	Poorly developed cerebellum
	Glioma	Malignant extension from pons
	Miller-Dieker syndrome	Hypoplasia of cerebellum, pons
Brain stem	Dandy-Walker syndrome	Dysplasia of inferior olivery nerve aplasia of cerebellar vermis
	Joubert syndrome	Anomaly of nucleus tractus solitarius
	Mobius syndrome	Multiple etiologies: necrosis of brainstem
Spinal column	Trauma	
	Vascular accident	
	Spinal muscular atrophy I	Autosomal recessive, 5q chromosome, degeneration of anterior horn cells
	Achondroplasia	Vascular obstruction
	Arnold-Chiari syndrome	Vascular obstruction; herniation of medulla and cerebellum
	Osteogenesis imperfecta	Compression of upper cervical cord
Muscle	Mitochondrial myopathies	End organ dysfunction
	Metabolic myopathies	
	Nemaline rod myopathy	
	Congenital myotonic dystrophy	
	Myotubular myopathy	
Neuromuscular junction	Congenital myasthenia	
	Infantile botulism	Infectious; end organ dysfunction
	Neonatal polio	Infectious; end organ dysfunction
Pulmonary	Cystic fibrosis	Excessive secretions; increased work of breathing
	Asthma	Excessive secretions; increased work of breathing
Miscellaneous	Congenital heart disease	Increased recirculation time
	Pulmonary edema	Increased recirculation time; increased work of breathing

at birth. Other, less common causes, usually seen in hypotonic infants, include myasthenia gravis, infantile botulism, and neonatal poliomyelitis.[30] Irregular breathing, central apnea, and hypotonia frequently complicate premature birth.

Upper airway collapse, high chest wall compliance, lower airway disease, and muscular weakness can cause obstructive apnea that may appear to be central apnea on recordings, but the respiratory effort may not be apparent if the child has tachypnea or if the gauges cannot pick up the signal. At least some episodes of central apnea may actually be mixed apnea with the central component preceded by a short obstruction sometimes obscured by rapid respiratory rate, motion, or poor or weak effort.[31]

Congenital heart disease, especially when associated with cardiac failure, can cause central apnea in the rare cases when it results in a prolonged circulation time. Central apnea has also been correlated with pulmonary edema, possibly because of increased work of breathing and eventual fatigue. The thick mucus associated with cystic fibrosis and asthma may cause difficulty with air exchange or potentiate airway collapse, which also can mimic central apnea.

Obstructive Sleep Apnea

Multiple mechanisms predispose infants to upper airway obstruction, including poor integration of the neuromuscular response, hypotonia of the upper airway, high percentage of time in REM sleep, and supine position. The brain and eyes are nearly adult size at birth, but the maxilla, mandible, and face are small and relatively undeveloped. The neck is short because of the small cervical vertebrae, and the larynx is seated high in the airway. The mandible is flexible and can be easily displaced posteriorly because of its horizontal placement, lax temporomandibular ligament, and absent mandibular fossa.[32] In addition, the tongue is large and fills the oral space for the first 5 to 6 months of life, necessitating nasal breathing.

The oblong shape of the infant chest and subsequent absence of rib recoil during expiration produces a neutral pharyngeal pressure instead of the positive pressure noted in adults. The infant breathes from a higher end-expiratory lung volume, which is determined by the length of expiration and expiratory braking (a mechanism that appears to prevent collapse of alveoli in the infant lung and maintain the FRC). This breathing mech-

Table 2. Causes of Obstructive Apnea

Level	Name/cause	Type of Defect
Suprapontine	Cerebrovascular accident	Muscular weakness; discoordination
	Cerebral palsy	Muscular weakness; discoordination
Brain stem	Arnold-Chiari syndrome	Vocal cord dysfunction
	Möbius syndrome	Dysfunction of cranial nerves
Spinal cord	Trauma	Discoordination or weakness of upper airway muscles
	Spinal muscular atrophy, all types	Upper airway muscular weakness during sleep
Muscle	Myopathies	Upper airway muscular weakness during sleep
Airway	Pierre-Robin/Treacher-Collins syndrome	Micrognathia
	Micrognathia	Decreased airway size
	Tonsillar/adenoidal hypertrophy	Decreased airway size
	Choanal atresia	Blockage of nasal airway
	Obesity	Decreased airway diameter
	Prader-Willi syndrome	Hypotonia
	Down syndrome	Hypotonia; decreased airway size
	Laryngomalacia	Obstruction by floppy laryngeal structure
	Tracheomalacia	Obstruction by floppy trachea
	Foreign body	Acute obstruction from inhaled object
Lung	Asthma	Thick secretions
	Cystic fibrosis	Thick secretions

anism disappears by age 3 to 4 months as chest wall compliance decreases, but it may persist in the presence of underlying lung disease.[33]

The work of breathing is also determined by the resistance to flow of the upper airway. This in turn is a function of the size and stability of the upper airway, especially when diaphragm contraction generates a negative force. Flow becomes tenuous if the airway is made smaller at any level at or above the larynx. Normally the tongue is moved forward during breathing by the genioglossus muscle, pulling the epiglottis forward. When the pharyngeal muscles relax during REM sleep and diaphragm-generated negative pressure increases, obstruction becomes more likely. Obstructive apnea is more common in disorders associated with airway narrowing or muscle hypotonia (Table 2).

Using polysomnography, a higher frequency of obstructive events has been identified in infants who experienced an ALTE and subsequently died from SIDS.[34] Studies have also shown that children who experienced an ALTE during infancy are at risk for airway obstruction and by age 5 years were often diagnosed with obstructive sleep apnea.[23] Another group of children with obstructive sleep apnea, normal after treatment with tonsillectomy and adenoidectomy, exhibited a recurrence of symptoms during puberty.[35] These findings suggest an anatomic or physiological predisposition to obstruction.

Sudden Infant Death Syndrome (SIDS)

SIDS is defined as the sudden death of an infant under age 1 year that remains unexplained after a thorough case investigation, including performance of a complete autopsy, examination of the death scene, and review of the clinical history.[36] Several mechanisms of SIDS have been postulated; the most popular theories include possible defects in the control of breathing and arousal deficits, airway obstruction with hypoxic events, and cardiac arrhythmia.

Arousal deficits have been implicated as a cause of SIDS. Most SIDS cases occur during the sleeping hours.[37] Arousal responses are normally depressed during REM sleep. Exposure to cigarette smoke, a known risk factor for SIDS, has been postulated as one possible cause of this defect; failure to arouse to hypoxia has been observed with nicotine exposure in animal models.[38] It has also been noted that repeated hypoxic episodes result in habituation to the insult with failure to arouse when confronted with hypoxia.[39] Findings on brain autopsy include abnormalities of the area of the infant brain stem associated with respiratory control.[40-42] Obstructive sleep apnea has also been proposed as the cause of some cases of ALTE and SIDS.[32,35] Significantly, SIDS is more common in families with a history of obstructive sleep apnea.[42] In addition, a prospective study noted that

airway obstruction occurred more frequently in infants who later died of SIDS.[34,43] Finally, autopsy evaluations in infants who have died of SIDS have found abnormalities consistent with chronic hypoxia, including abnormal astrogliosis, increased pulmonary arteriolar muscle, abnormal retention of adrenal brown fat, extrauterine growth retardation, elevated brain lactate, and high vitreous humor levels of hypoxanthine.[44]

Cardiac arrhythmias have been documented as one cause of sudden death. Prolonged QT syndrome has been the most prominent abnormality associated with sudden death in infants, found in one study in one-half of the cases of SIDS investigated.[45] Later studies identified a spontaneous genetic mutation.[46]

SIDS may be the final step in a multifactorial process. The "triple-risk" hypothesis proposes that SIDS results from a confluence of events in (1) a vulnerable infant, (2) exposed to exogenous stressors, (3) during a critical development period. This hypothesis has been disputed recently, however.[47] Ultimately, prevention of SIDS hinges on the ability to recognize risk factors, either clinically and biochemically, in time to allow effective intervention.

Chemical Abnormalities of Breathing

Congenital central hypoventilation syndrome (CCHS) is a disorder of the central chemoreceptors causing hypoventilation, primarily during NREM sleep, along with a depressed response to hypoxia. Severely affected infants may also hypoventilate during wakefulness.[48] Infants with this disorder may also exhibit autonomic nervous system involvement, Hirschsprung's disease, cardiac abnormalities, and blood pressure anomalies.[49] Interestingly, because the mechanoreceptors of the joints still continue to function, respiratory rate increases with exercise.[50] Moving the legs during sleep has been proposed as a potential treatment, but at present infants with this disorder require nocturnal ventilation.[51] These infants come to medical attention in the neonatal period when they become apneic or experience respiratory arrest. CCHS is extremely rare, however, and most infants who hypoventilate during sleep have underlying, unrecognized neuromuscular disease or upper airway obstruction. With long-term abnormalities, children with upper airway obstruction become habituated to the elevated CO_2 level.[52]

Abnormal peripheral chemoreceptors have been implicated as a cause of hypoventilation in Prader-Willi syndrome (a genetic disorder associated with deletion of the long arm of chromosome 15).[53] Patients with this disorder are usually obese (because of associated hyperphagia) and hypotonic and have a high incidence of sleep-disordered breathing. The sleep hypoventilation is at least partly attributed to a peripheral chemoreceptor defect.[54]

CONCLUSION

Control of breathing in infants and children develops during a period of marked change. A multitude of difficulties may be encountered during the transition from fetal life to continuous breathing and then in the ongoing maturational processes that occur in all involved organ systems (brain, muscles, and respiratory system). All of these changes must be precisely coordinated for the child to survive and thrive. Continuing research into the normal process is needed to better define and then investigate abnormalities. Some abnormalities have been defined, but the possible connections between these abnormalities and the pathological processes discussed in this article—particularly SIDS—remain unknown.

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